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## **INDENA AHEAD OF THE GAME IN NEW FIELDS OF RESEARCH**

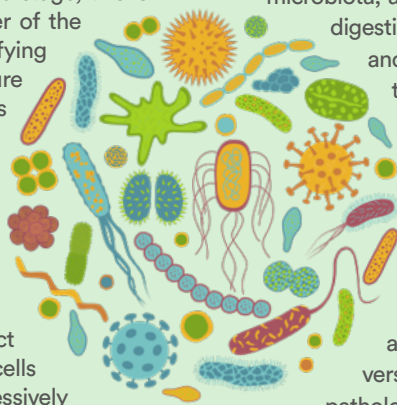
*by Antonella Riva*

People generally consider themselves autonomous living beings but scientific research in recent years has revealed that there are micro-organisms whose contribution is essential for our health and well-being. This "21st century organ" is the microbiota. Not only is each one of us literally inhabited by micro-organisms, we are also surrounded by them as if enveloped in a "microbial cloud". Infinite varieties of microorganisms are associated with numerous conditions, such as allergies, diabetes, obesity, arthritis, inflammatory bowel disease and even certain neuropsychiatric disorders. To maintain a healthy state of well-being therefore, it is essential that there is a strong, well-coordinated interaction between these micro-organisms and the body which hosts them.

Individuals are born with a distinctive microbiome which remains a badge of identity throughout their entire lifetime. In fact, our microbiota is born along with us and is born the way we are born. Microbes begin to conquer the human intestine at birth; the infant is in fact exposed to the complex population of microorganisms residing in the vagina. Studies have shown that the microbiota of the mother's vagina bears similarities to the intestinal microbiota of the infant, suggesting an important influence of that very first contact, at the moment of delivery, in the development of the individual's bacterial flora. Subsequently, in the first year of life, the composition of the microbiota is enriched with new elements on interaction with the environment and as a result of contact with the mother during breastfeeding. Then from the second year of life, the baby's intestinal microbiota presents more and more like that of a young adult as it begins to stabilize.

Just how big is the microbiota of an average adult? Let's look at the numbers and topographic details. Our bodies cohabit with a number of microorganisms amounting to  $3.9 \times 10^{15}$ . The highest concentration and greatest biodiversity occupy the gastrointestinal tract which provides defence against external agents; for this reason, it is colonized by a multifarious community of bacteria able to orchestrate the immune response. So much for the number of bacteria. If we consider their genetic heritage however, we note that the enteric microbiota alone contains a number of genes at least 100 times higher than that of the human genome. This is because our microbiota is involved not only in immune defence but acts as a crossroads for the metabolism of amino acids and carbohydrates and synthesizes vitamins.

In the face of this complexity, the scientific community has joined forces to share research programs and make funds available. The Human Microbiome Project was launched by the NIH back in 2007. There have also been numerous projects in Europe focused on the organization of databases for the identification and attribution of the "microbiomic spectrum". To characterize and study the human microbiome means analysing the genetic material of the microbiota and to this end there are two common routes to follow; the first step consists in processing the biological samples and extracting the DNA, then, at a second stage, this is sequenced in order to ascertain the order of the nucleic bases along the DNA chain, identifying the strain and its number. But why measure the microbiome? Because its modifications accompany the various stages in our lives and, probably its imbalances are linked, for example, to functional disorders of the gastrointestinal tract and the metabolic syndrome; nor can anxiety and chronic neurodegenerative diseases be ruled out either. Certainly physiological aging is one of the phenomena that affect the malfunction of the microbiota: the cells and the immune system degrade progressively and unceasingly, sparking processes and changes that affect the general health of the individual. One of the most dangerous is silent inflammation that, often asymptomatic or neglected, can become chronic triggering or facilitating some of the world's most serious and common cardiovascular, oncological, neurodegenerative, gastrointestinal diseases.[1] The microbiota can also be affected in a positive but also negative way by a person's lifestyle, environment, nutrition and medicinal drugs. Use of medicines for example may indeed help to manage certain diseases; prolonged use however can lead to damage, especially to the gastrointestinal system, which, when overloaded, struggles to cleanse the body of harmful substances. In a recent work, published in the journal *Nature*, over 1000 drugs and 40 species of intestinal bacteria were examined.[2] Researchers found that changes in the composition of the microbiota were associated with 24% of the drugs developed to target human cells only; these included antidiabetics, proton-pump inhibitors, non-steroidal anti-inflammatory drugs and atypical antipsychotics. The conditions that affect the microbiota can induce "dysbiosis", or the imbalance of the microbial system. Dysbiosis is becoming more and more a real therapeutic target, an example is Small Intestinal Bacterial Overgrowth. SIBO is a clinical condition closely related to a wide range



of gastrointestinal symptoms; these may be associated with risk conditions such as anatomic alterations, irritable bowel syndrome, metabolic abnormalities, systemic dysfunctions, such as celiac disease or Crohn's disease, and even pharmacological therapies. First-line treatment for SIBO is antibiotics, but the high recurrence rate of this disorder leads researchers to assess the potential role of well-tolerated products of natural origin with anti-inflammatory and antibacterial activity.

Nutrition can be a valuable ally therefore; active natural substances integrated into the diet have been shown to improve certain functions of the organism. These substances may be botanical extracts but also probiotics; they act out on the microbiota and, consequently, on the universe of biological reactions connected to it. Turmeric, Boswellia, artichoke and ginger extracts, for example, have been shown by many clinical studies to be effective for gastrointestinal health. Probiotics have also shown positive effects on the microbiota of the intestine and can exert a positive influence on the structure of the microbiota, encouraging beneficial bacterial species and counteracting the problematic ones. This is a key point for the health of the individual since the microbiota, as has been shown, has an impact on aging, digestion, the immune system, mood changes and on cognitive functions. It follows that the health of the microbiome is not only fundamental for the health of the individual but the microbiota itself can be the means with which to act on the health of the individual. In fact, several research projects have been underway for some time, with the common aim of identifying how to optimize the relationship between an individual and their microbiome (and vice versa) thereby prevent or alleviating certain pathologies.

Once again, Indena is in the vanguard of this movement. Sure in the standardization and the high phytochemical definition of its botanical ingredients, Indena is pursuing experimental research initiatives; these include the study of interaction between the microbiota and single ingredients, the blend of ingredients capable of modulating different species, and the combination of botanical ingredients with probiotics. Indena regards the microbiota as one of the fundamental targets to reveal the "gastrointestinal pharmacodynamics" of its botanical extracts. This is a wide-ranging and promising area, in which Indena will continue to invest for years to come, working alongside major international research institutes. Starting out from Nature itself, the goal is to contribute to the improvement in the quality of people's lives following a biomimetic approach; with Nature as inspiration, Indena will continue to develop new products and explore new uses for existing ones. As ever, *Science is Our Nature!*

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Nutra

# MERIVA<sup>®</sup>, PRODIGEST<sup>®</sup>, CASPEROME<sup>®</sup>: A NATURAL DIFFERENCE IN GASTROINTESTINAL HEALTH

Today's stressful lifestyles together with increasingly widespread poor eating habits are leading to a growing incidence of digestive and intestinal disorders. This clearly has an effect on consumers, who are increasingly looking for natural remedies to cope with this type of disorder. It is indeed a market segment displaying a significant growth trend and promises yet further growth in the future. Considering the limits in effectiveness of most conventional therapies used to combat digestive conditions, it is hardly surprising that over 50% of people with disorders such as functional dyspepsia seek out alternative, and more *natural* remedies.

Nature itself provides us with an inestimable treasure on which Indena has always drawn in its quest to develop high quality extracts with a solid scientific background. And to meet the needs of consumers in this particular area of health, Indena has developed the products: Prodigest<sup>®</sup>, Meriva<sup>®</sup> and Casperome<sup>®</sup>. All three ingredients have showed an excellent profile of effectiveness in improving digestion and intestinal health.

Prodigest<sup>®</sup> is a combination of the standardized extracts of artichoke leaves (*Cynara cardunculus* L.) and ginger root (*Zingiber officinale* Rosc.) which is the fruit of Indena innovation and experimentation. This combination has been shown to be effective both in improving the functionality of the gastrointestinal tract, in particular in favouring gastric emptying, and in giving relief to disorders caused by conditions with a significant impact on the quality of life, such as functional dyspepsia, which involves swelling, digestive difficulties and diarrhoea.

Gastrointestinal disorders are related not only to lifestyle and diet but also, as several studies show, to forms of latent inflammation that often originate from minor complaints that, if underestimated or neglected, may over time become chronic.

Meriva®, the curcumin phytosome produced by Indena has given excellent results in this area. Meriva® is an ingredient used worldwide in the health food sector and is present in many food supplements available on the Italian market. Launched in 2007, it is today the only such ingredient in the world documented by more than 30 clinical studies to support its use in combatting various types of low chronic inflammation.



These include the inflammatory conditions of the digestive system and that most important gland associated with it, the liver. For example, a recent study involved subjects with Non-Alcoholic Fatty Liver Disease (NAFLD), a condition which affects 30% of the general adult population and 60-70% of diabetic patients. It is predicted to become the leading cause of liver transplants by 2020. In addition to being well tolerated, Meriva® showed an excellent safety profile and the ability to improve liver health in eight weeks, reducing serum lipids and uric acid concentrations in the subjects involved. [1, 2]



Lastly, *Boswellia serrata*, the Indian incense extract from which Indena has developed Casperome®, is the only formulation on the market supported by clinical studies that demonstrate its effectiveness in improving gastrointestinal disorders such as Irritable Bowel Syndrome (IBS). [3] This effectiveness is above all due to the totally food grade Phytosome® delivery system, which significantly increases the bioavailability and bio-absorption of the triterpenic acids contained in *Boswellia serrata*.

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**Meriva®** Meriva® is the leading brand in the turmeric derivatives sector, standardized to contain the entire bouquet of curcuminoids.

The Phytosome® delivery system, using only food grade excipients, ensures levels of safety, tolerability and efficacy which have been demonstrated in over 30 clinical studies on over 2000 subjects.

Its efficacy profile has been validated in over 10 health conditions including joint and bone health; it is effective also in sports nutrition and in all those conditions that have their origin in chronic silent inflammation, such as gastrointestinal disorders.

MERIVA® THE LIFE GUARDIAN™ is effective in regulating inflammatory processes and the fact that it may be taken for long periods makes it a real boon for health maintenance programs.

Meriva® is formulated with the Phytosome® delivery system (Nature as Measure™): each stage in its development has drawn on Nature as a model, measure and mentor to guarantee the suitability of any innovation in the world of health-foods.

# GREEN GOLD: USING BERGAMOT TO COMBAT HEART DISEASE

Cardiovascular diseases are the leading cause of death and disability world-wide according to the most recent data from the World Health Organization: over 17 million deaths each year, 31% of the total. Although strokes and heart attacks are the principal triggers of these diseases, lifestyle habits such as smoking, poor nutrition, physical inactivity and alcohol abuse can provoke high blood pressure, an increase in blood glucose levels, weight gain and obesity, conditions that threaten the health of the heart. [1] According to the American Heart Association, [2] high levels of cholesterol, triglycerides and LDLs are also associated with an increase in the incidence of atherosclerosis and coronary heart disease. They recommend prevention by adopting wholesale lifestyle changes and emphasize the importance of diet enrichment with a variety of nutrients.

Nature once again is the source of valuable substances, which are effective in the prevention and in some cases in the control of certain conditions relating to cardiovascular health. Many scientific studies support the strong correlation between a diet rich in flavonoids and the reduction of cardiovascular risks. In particular, *Citrus bergamia* Risso et Poiteau, known commonly as bergamot, has shown an antioxidant and anti-radical action, arousing the interest of researchers.

One of the world's most popular teas, Earl Grey is flavoured with Bergamot oil derived from *Citrus bergamia* Risso et Poiteau, a plant endemic to Calabria. The traditional use of bergamot has been rediscovered due to its natural and almost unique pattern of polyphenols, present in the juice, albedo and flavedo. Its unique composition has shown antioxidant, hypoglycemic and hypolipidic activity, with positive effects in regulating the metabolic syndrome and offsetting cardiovascular disorders. The exceptional properties of bergamot have led to it being called "green gold" and numerous studies show that it is a safe alternative for those who are intolerant to statins. [3-6]

This prized citrus fruit from Calabria has been used by Indena to develop Vazguard™ - created with the application of the food grade delivery system Phytosome® to a highly standardized extract of the polyphenolic fraction

Vazguard™

Vazguard™ is the Indena extract of bergamot (*Citrus bergamia* Risso et Poiteau, exclusively from plantations in Calabria) standardized to contain 11-19% of total bergamot flavonones using HPLC.

The recommended dose is 500mg twice a day and the Phytosome® delivery system optimizes the biological absorption of polyphenols, normally characterized by low solubility.

Clinical studies show that Vazguard™ is effective in modulating total cholesterol, HDL, LDL, triglycerides and glucose levels, through antioxidant, hypoglycemic and hypolipidemic action. These characteristics make it particularly suitable for use against metabolic syndrome and in any condition that might impair the maintenance of good cardiovascular health.

of bergamot, which optimizes the bioabsorption of polyphenols, usually characterized by poor solubility both in water and in organic solvents.

Vazguard™ is standardized to contain 11-19% of the total flavonones (HPLC) of bergamot and is supported by clinical data that certify and strengthen its



safety and efficacy profile. After only 30 days of supplementation, Vazguard™ was effective in modulating total cholesterol (tCol), low-density lipoproteins (LDL), triglycerides (TG), high-density lipoproteins (HDL) and blood glucose. [7]

Another notable success story for our Indena researchers: Vazguard™ acts on all the parameters involved in cardiovascular prevention, a result that is usually achieved only with the use of a mix of natural or synthetic substances. This makes it a valuable aid in safeguarding and improving health.

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## INDENA AND SPORTS NUTRITION

People who practice sport, even at moderate level, frequently supplement their diet to improve performance, reduce exhaustion or prevent small injuries that often follow the fitness session, be it recreational or competitive. Edible plants undoubtedly offer an extraordinary source of valuable substances which can promote general well-being and, consequently, complement the nutrition of sportsmen and women.

Indena has long been involved in sports nutrition, and certain Indena ingredients have shown very convincing results at the clinical level.

The effectiveness of Meriva® in sports nutrition is supported by significant clinical results. These show how Indena's phytosome curcumin can be a valuable aid for joint health and to address the inflammatory pain, swelling or stiffness that can follow exercise in a variety of sports, even when practiced intensely, as in for example rugby and cycling, through the neutralization of oxidative stress and the modulation of pro-inflammatory cytokine homeostasis. Meriva® has also been shown to improve physical strength and performance in healthy subjects, helping them to maintain muscle mass. The most recent results come from a double-blind, placebo-controlled study on men demonstrating that the use of Meriva®, even for short periods, may be useful in maintaining the integrity of the

gastrointestinal barrier and physiological responses during the stress phase that accompanies physical effort in conditions of high heat and humidity. It should be noted that supplementation with phytosome curcumin reduces the risk of heat stroke exertion, especially in non-acclimatized subjects, since it also improves the physiological stress index (PSI) by moderating the increase in body temperature and heart-rate that occur during physical activity. In the last decade, several supplements have been tested to verify their effectiveness in improving the functions of the gastrointestinal barrier and system-level physiological responses, but none proved able to act on both simultaneously. [1]

Quercefit™ is another product that has shown to be effective in sports integration. Once again, Indena's Phytosome® delivery system has been successfully applied to one of the best-known and important flavonoids, quercetin, showing an increased uptake of up to 20 times in a pharmacokinetic study conducted on healthy volunteers. The clinical efficacy of the ingredient emerged in a controlled study conducted on amateur triathletes using the "Sprint" race format (a 750 m swim + 20 km bicycle + 5 km run). [2] Quercefit™ statistically improved the resistance of those who took it, enhancing performance and recovery by alleviating pain, cramp and other disorders. A strong antioxidant effect was demonstrated.

Sports performance can also be affected by the health of the digestive system. Effort during physical activity affects the blood flow which can induce the onset of a weak temporary inflammation. Exercise, especially when it involves fatigue, can lead to the repetitive use of abdominal muscles in the stomach area: this generates pressure on the gastrointestinal tract and can aggravate certain disorders.

Prodigest® can be useful in this type of condition, as it capitalizes on the synergy between artichoke and ginger extracts. Indena redesigned these two well-known extracts in the development of Prodigest® creating a product now accredited by exhaustive clinical data which supports both the function of gastric emptying and effective relief from the disorder.



### Quercefit™

Quercefit™ is a 100% food grade formulation of quercetin extracted from *Sophora japonica* L., standardized to contain 34-42% quercetin (HPLC).

The Phytosome® delivery system optimizes the bioabsorption of flavonoids. Compared to other non-formulated quercetin extracts, the Indena extract has been shown to be up to 20 times more bioavailable and more effective at the same dosages.

Clinical studies show that its action can improve conditions resulting from significant oxidative stress, such as intense physical activity sessions.

This makes it a valuable aid in sports nutrition, for enhancing performance in sport and reducing recovery times.

### Prodigest®

Prodigest® is produced from a combination of the artichoke leaf extract (*Cynara cardunculus* L.) and the unique ginger root extract (*Zingiber officinale* Rosc.). Their action together is more effective than that of the two extracts taken separately.

Clinical and toxicological studies of the combination demonstrate its functionality and efficacy in gastrointestinal disorders, favouring gastric emptying and relieving the general discomfort which is associated with this condition.

The extract of *Boswellia serrata* whose properties are well-known in traditional medicine may indeed also be considered an effective support in sports nutrition. There are a number of studies to support the rationale for its use in musculoskeletal disorders, as it inhibits the molecular mechanisms underlying these conditions.

This was the background for the development of Casperome® by Indena researchers who, for the first time, documented effectively the potential of this natural product for sportsmen. An initial clinical study conducted on young rugby players with acute knee pain and inflammation due to sports trauma has shown that supplementation with Casperome® can be an effective and safe integrated approach for the treatment of osteo-muscular pain and inflammation: undergoing the treadmill test, the subjects who took the product had inflammation markers that were lower than the control subjects and travelled a greater distance without pain. [3]

Furthermore, analgesic use was significantly less in the Casperome® group than in the standard control group. A recently published study highlighted the efficacy of Casperome® in healing Grade 2 ankle sprain, suggesting that there may be a potential benefit in relieving the trauma associated with sport and in reducing the use of symptomatic drugs. [4]

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### Casperome®

Casperome® is the result of modern research on *Boswellia* which clearly highlights the clinical efficacy of the extract, the significant presence of the entire bouquet of triterpenoid acids and an optimization of bioavailability.

The extract Casperome® is HPLC standardized to contain ≥25% of triterpenoid acids, whilst the 100% food grade Phytosome® delivery system ensures good oral absorption.

Intake of Casperome® leads to a significant decrease in perceived pain, particularly in chronic conditions related to inflammatory states, including respiratory difficulties, and improves joint function. It is also effective in gastrointestinal disorders, as it relieves the symptoms of irritable bowel syndrome.

These results are supported by seven clinical studies, which also confirm the safety profile of the extract.



# NATURE AS MEASURE™

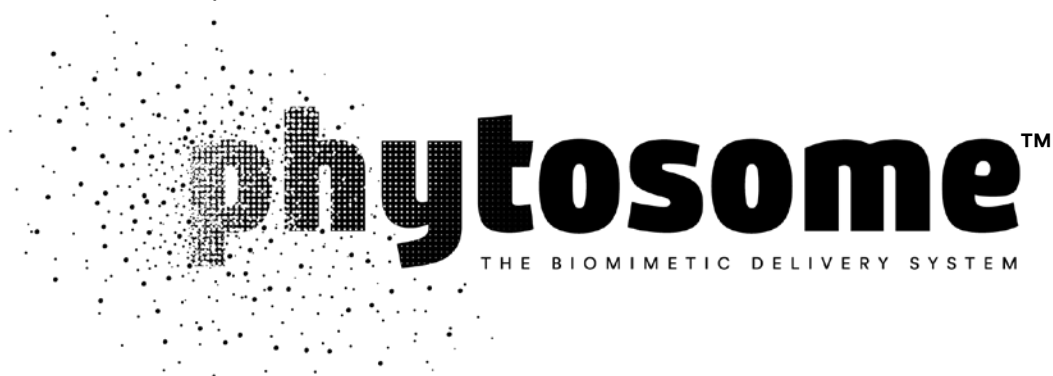
Plants are an invaluable source of substances prized for their biological activity. Many properties of these substances have been known since ancient times and still form the basis of traditional medicine. Many of these components, however, display poor solubility in water and a low level of absorption by the intestines; in addition, they may be naturally available in complex shapes and matrices and often need to be optimized to improve physiological absorption levels.

The bioavailability of substances has always presented a daunting challenge for researchers and producers of botanical derivatives. Alongside this, the sometimes cryptic and deliberately complex approach and language used by some manufacturers risk confusing consumers who in some cases, without expert guidance, may be unable to evaluate the quality and functionality of a product based on botanical derivatives.

With the scientific confidence built up in almost a century of experience, Indena has long argued that acting only on the bioavailability side is at best reductive: the real objective should be to optimize bio-absorption levels, while maintaining the safety efficacy and tolerability profiles of the extracts exactly high. Indena has indeed achieved this goal by applying the biomimetic principle Nature as Measure™.

Biomimetics, a term that derives from "bios" (life) and "mimesis" (imitate), is the science that studies Nature and natural phenomena; it aims to understand how they work and to imitate their design, patterns and features, with the ultimate purpose of solving human problems. Biomimetics is, in a nutshell, "innovation inspired by Nature" and to epitomize this concept Indena has coined the term: Nature as Measure™. Nature, by necessity, has already solved many of the problems with which man has to deal but the plants and microbes are engineers with long experience; they have already discovered what works, what is appropriate, what lasts over time and why. Nature therefore is the standard by which we judge the appropriateness, sustainability and also the formal strategic and ethical correctness of any technological innovations in the process and the product.

Nature as Measure™ is also the fundamental principle with which Indena develops its active ingredients based on natural extracts with the Phytosome® formulation.



Introduced into the field of food supplements over 20 years ago, Phytosome® is the pioneering delivery system developed by Indena able to improve the bioabsorbability and pharmacokinetic profile of active compounds of natural origin using only food grade excipients such as lecithin. Lecithins are natural surfactants that take part, together with bile salts, in the physiological process of absorption of lipophilic compounds and constitute the double phospholipid layer of cell membranes; they make

it easier for the intestine, for example, to absorb compounds which are only slightly soluble in water. Lecithin acts as an inhibitor of self-aggregation, allowing the poorly soluble compounds in a dispersed state to be absorbed more rapidly.

Phytosome® represents the natural approach to optimize the solubility and bioabsorption of phytochemicals by reducing the self-aggregation of active compounds. The food grade matrix of Phytosome® enables the original chaos, disposition and complexity of natural substances to be maintained, without any recourse to chemical derivatives or new chemical entities, nor to pharmacological adjuvants or to structural changes in the ingredients, thereby maintaining their safety and tolerability over time.

Nothing is left to chance. Each Phytosome® formulation is specifically designed during the research and development process, to maximize the bioavailability of the selected botanical extract. The functional and technological properties of the final product are optimized through the modulation and control of all the different process factors.

The physical properties and technological characteristics of Phytosome® make it possible to optimize the dissolution profile and, consequently, the bioavailability of natural active ingredients; at the same time, they facilitate the formulation process, enabling Phytosome® to be used easily in varying dosages. Strict pre-clinical and clinical trials reveal that Phytosome® formulations show better solubility in gastrointestinal fluids, and a better pharmacokinetic profile than unformulated botanical extracts.

Alongside the knowledge and expertise of Indena researchers, the company boasts state-of-the-art technological equipment and a continuous commitment to quality. This enables Indena to produce the Phytosome® formulations on an industrial scale ensuring the reproducibility of the matrix of the natural component, every batch of which is controlled and guaranteed.

## Phytosome®

- 100% food grade ingredients
- Absence of synthetic or adjuvant ingredients
- Improves bioabsorption of natural phytochemicals
- Unique technology and know-how spearheaded by Indena over 20 years ago
- Tailor-made for selected natural components
- Industrial scale production possible
- Absence of nanoparticles
- Can be formulated in the most common dosages
- Patented technology
- Supported by preclinical and clinical documentation



Pharma

## FROM GRAMS TO TONS INDENA IS THE IDEAL PARTNER

2018 has been a very important year for Indena Custom Services. In fact, delivered perfectly on schedule and capitalizing on the company's long experience in the field of high containment, Indena has inaugurated its new Kilolab which is designed for HPAPI production, whether by natural, semi-synthesis and total synthesis. The new Kilolab has been engineered to handle the production of toxic substances characterized by an occupational exposure limit (OEL) of 20 ng/m<sup>3</sup> implementing the most stringent safety procedures to protect the people who work with it. It provides the best and most innovative technologies for containment in order to prevent any accidental release of high power materials outside the containment areas. The level of containment also allows the production of payloads with toxins, such as maytansines, used by the makers of antibody-drug conjugates (ADCs).

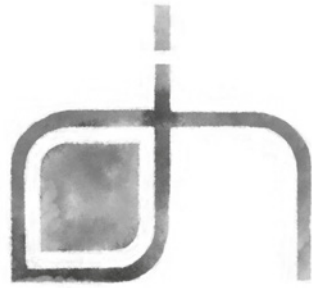
Analysis and research laboratories form part and parcel of the new plant which enables all project phases, from development to production, to be managed together. The new Kilolab is equipped to handle cGMP lots for clinical trials up to industrial quantities. It can manage full-synthesis processes and contract manufacturing services on HPAPIs that include extraction, isolation, purification and also synthetic modifications of active pharmaceutical ingredients. The new Kilolab has the technical capabilities to manage a wide range of compounds classes, than the previous model; these include derivatives from fermentation and from total synthesis as well as highly toxic components.

Construction of a multi-purpose GMP pilot plant will be completed later in the year. This is designed for the grinding, extraction and purification of toxic plants and will be fitted with chromatographic columns for purification and reactors for API production both with semi-synthesis and total synthesis. This equipment is in itself a microcosm of all Indena technologies.



Also part of the investment plan is a capacity increase in spray-drying with organic solvents. A new highly flexible medium-scale spray-dryer will add to the technology Indena has been using for more than twenty years.

Although traditionally perceived by pharmaceutical companies only as a producer of extracts of natural origin, Indena is in fact able to manage API production both with semi-synthesis and total synthesis. Custom Development and Manufacturing has always been a key activity for Indena and from now on the company will be able to develop even more tailor-made projects for its customers, providing a unique added value on the market in terms of skills and technologies.



Corporate

## OUR JOURNEY THROUGH SUSTAINABILITY

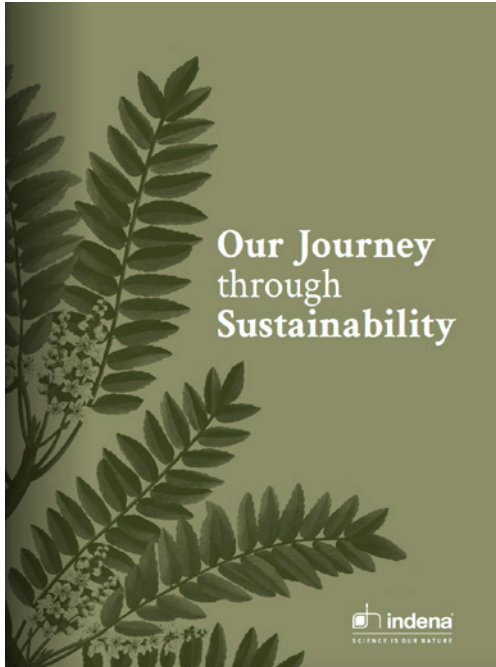
The commitment of Indena to the sustainable management of the supply chains of botanic raw materials and to its production sites is continuous. "Our Journey through Sustainability" is a new publication which charts the intentions, the progress and the results of this work. It tells the story of the journey undertaken from the birth of the company and its relationship with Nature which has been both a source of inspiration and an essential resource. Drawing on passion, dedication, science and technology, Indena has always known how to employ the highest production standards to garner from Nature and create reliable products that can improve people's health and lifestyle. Safeguarding Nature and making a social and economic contribution to the communities involved in the collection of the many species that Indena markets, lie at the heart of the projects undertaken within the Sustainable Sourcing Program. These projects include a contribution to the school system in regions of Madagascar where *Centella asiatica* is harvested, improvements to the supply chain and working conditions with *Boswellia serrata* in India and the implementation of a sustainability program in Tanzania for the *Terminalia sericea* chain.

Respect for the ecosystem and the environment nowadays calls for an ever-increasing effort to reduce the environmental impact of production sites. Indena has been actively engaged for years in this endeavour which has led to significant results in its main facilities.

CO<sub>2</sub> emissions have been reduced by around 10% over two years through the introduction of a methane-based cogeneration plant in 2015 at the Settala production site near Milan. Figures relating to the extraction of biogas, its transportation to the plant - including any losses - the combustion of natural gas, the production and transport of electricity have been calculated using Life-cycle assessment techniques.

The corporate transport service is used by 60 site workers, who otherwise would cover an annual total of 450,000 kilometres. Calculated over ten years, this is equivalent to a reduced emission of 70 tons of CO<sub>2</sub>. The construction of a new energy-efficient building at the French facility in Tours, has led to energy savings of over 60 MWH per year, equivalent to an annual CO<sub>2</sub> reduction of 54 tons.

In addition, by recycling solvents used in pharmaceutical applications, with a rectification plant which has existed at the Settala site since 1970, it has been calculated that over a ten-year period, the emission of about 330 tons of Non-Methane Volatile Organic Compounds (NMVOC) has been avoided, an expression of the potential impact of ozone (Photochemical ozone creation potential).



Use of hydrochloride solvents has been reduced by about 75% in ten years at the Tours plant by choosing to use biomass from organic sources or from crops whose cultivation follows an agricultural system with low environmental impact. Another factor that can be included in the *Reduce, Reuse, Recycle* principle is the use of exhausted biomass as soil fertilizer (4500 tons/year in Settala, 3200 tons/year in Tours, 1200 tons/year in Palestro), as animal feed (3000 tons in Tours, 1000 tons/year in Settala) and for the production of biogas (800 tons/year in Tours).

These are just some of the results of the implementation of a sustainable management system attested by the ISO 14001 certification obtained for the production sites of Italy and France. As regards the protection of safety and health, OHSAS 18001 certification has also been granted. As evidence of this, the company is committed to the entire elimination of all asbestos from the production sites of Settala, Milan and Palestro and 95% from the Tours site. Asbestos removal must be completed by 2028 according to European law.

Indena will continue in this endeavour by implementing supply chain monitoring, supplier audits and new local projects. Production processes will continue to be analysed to achieve even greater efficiency and further reduce environmental impact. "Our Journey through Sustainability" also hopes to make a contribution to the achievement of the Sustainable Development Goals promoted by the United Nations and in particular to Goal 12 regarding responsible consumption and production.

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## THE MARKET CHALLENGES OF DNA

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Authenticity and traceability have always been key elements in guiding the choices of the most vigilant producers and consumers. It is a field in which Indena has always been ahead of the game.

In fact, although it is true that the plant kingdom is a vast and precious source of botanical species from which to obtain extracts able to support a healthy lifestyle and wellbeing in general, an essential part of this is the correct identification of these species; this should start even in the early stages of research and continue through all phases of the production process right up to the product batches. The certainty that a species in question is exactly the right one can be ensured through different analysis techniques but one of these alone may not always be adequate, which is why Indena adopts an orthogonal approach.

To date, there are two basic analytical tests: botanical identification (both

macroscopic and microscopic) and chemical identification, which takes place through analytical techniques for the characterization of secondary metabolites. For many plants the first may be sufficient, but in some cases it is necessary to resort to more in-depth tests that, sometimes may involve analysing the DNA of the plant itself.

Indena, Hyris and the NHP Research Alliance (TRU-ID) have signed a strategic collaboration agreement for the integrated development of test kits for DNA authentication in plant extracts and in products of natural origin in which they are used.

Indena's contribution to this project is fundamental as it brings to the table a wealth of resources and knowledge on botanical material; these include the preparation of herbarium vouchers with auxiliary information on its supply chain, professional taxonomic IDs, DNA sequences for the development of genomic ID methods on the Hyris platform, and the support of nuclear magnetic resonance (NMR) for chemical fingerprinting.

The bCUBE® from Hyris, a miniaturized and portable instrument for nucleic acid analysis, makes this possible. Incorporating all the hardware, software and reagents required for the analytical process, this fully portable laboratory maintains the accuracy of the results, reducing the times and costs normally involved with traditional methods.

Authenticity has always been a key element in the quality process of all Indena products. By virtue of its pharmaceutical background, genomic tests are used not only for APIs, but they were even employed in the field of supplements for particularly problematic species years before the Schneiderman case. Indeed way back in 2011 at the International Symposium of AOAC Europe Section in Nuremberg, Indena presented a poster illustrating the application of DNA analysis to eight species of Echinacea found in North America.\*

A large proportion of Indena products have already been DNA tested; these include the following genera: *Actea*, *Curcuma*, *Cynara*, *Echinacea*, *Eleutherococcus*, *Equisetum*, *Euphorbia*, *Ginkgo*, *Harpagophytum*, *Illicium*, *Kalanchoe*, *Panax*, *Silybum*, *Taxus*, *Vaccinium*, *Vitis*. The work does not end here, however, but continues in a constant effort to increase the quality level of the botanical extracts market.

INDENA DNA TESTED is a special logo created to assure Indena partners that the vegetal raw material used for the production of a specific extract has been "DNA tested".



The stakes may be raised and new challenges launched by the market, but Indena welcomes them and, drawing on a wealth of knowledge and researcher expertise, transforms them into opportunities.

\* "Different analytical approaches of authentication of Medicinal Plants: a case study the identification of *Echinacea* spp. Roots". 2011. C. Bonardi, V. Gualdi, R. Iguera, N. Fuzzati, I. Losini, P. Piffanelli. International Symposium of AOAC Europe Section in Nuremberg.



## Personal Care

# CENTELLA ASIATICA ENTERS A NEW ERA

A new study dedicated to *Centella asiatica*, a medicinal plant also known as "gotu kola", has been published with the aim of crossing new boundaries of use for a plant already widely used in traditional medicine.

*Centella asiatica* is native to the wetlands of Southeast Asia and belongs to the Apiaceae family; it has been used for centuries in traditional medicine because of its anti-bacterial, anti-viral, anti-hypertensive, diuretic, anti-ulcer and anti-inflammatory properties which are so powerful that it can help heal lesions caused by leprosy. [1] The active compounds are asiaticoside, madecassoside, asiatic acid and madecassic acid which, together, promote the synthesis of collagen, regulate inflammation by normalizing the hyperproliferation of keratinocytes and are able to restore the natural homeostasis of the epidermis. [2]

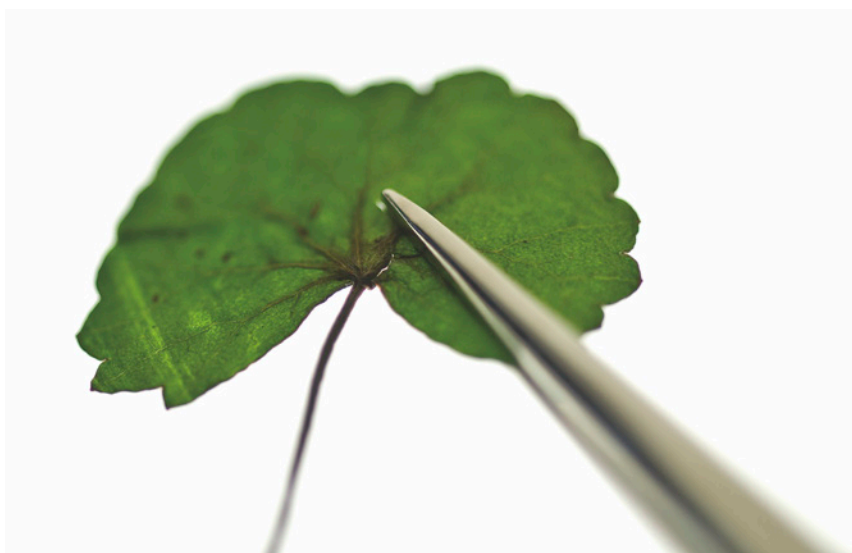
In Western medicine *Centella asiatica* is used mainly in its purified triterpenic fraction, *Centella asiatica* Selected Triterpenes (CAST), with a variety of both preventive and therapeutic applications. [3] Its versatility relies on various inter-connected mechanisms: the control of oedema and capillary filtration, its antioxidant effect, anti-inflammatory action, modulation of the production of collagen, migration of local growth factors and angiogenesis. [3] Recently anti-glycation properties have also been reported, [4,5] a process that has an active role in skin aging.

In addition to the traditional triterpenic fraction widely used in the pharmaceutical and cosmetic fields, Indena has developed other products derived from *Centella asiatica*.

These are slightly different fractions (again with a majority terpenic base) with characteristics of well-characterized biological activity: Centerox<sup>®</sup>, documented for increasing the expression of laminin-5, and Centevita<sup>®</sup>, which has shown the aforesaid anti-glycation activities. Indena is particularly interested in researching this plant and works alongside the world's most influential expert on *Centella asiatica*, François-Xavier Maquart. In his contribution to the extensive review, Dr Maquart highlighted the potential new cardiovascular and neurological uses of *Centella asiatica*.



*Centella asiatica* is known for its effectiveness in modulating the synthesis of collagen and for its direct activity on fibroblasts during the healing process. [3,6,7] In the cardiovascular field, for example, *Centella asiatica* has also proved to be effective on atherosclerotic plaques, to prevent thrombotic or embolic complications by increasing the density and stability of atherosclerotic echolucent plaques in patients with atherosclerosis. [8] The changes induced by Centella in the composition of the plaques are independent of lipid and cholesterol levels, as well as other factors related to atherosclerosis such as hypertension, obesity and glucose intolerance. [8]



In addition, the plant has also shown neoangiogenic properties in both animals and in vivo trials: [9-13] this activity is linked to the expression of angiogenesis regulation genes, such as the vascular endothelial growth factor (VEGF) and fibroblast growth factor (bFGF or FGF2).

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In neurology, traditional medicine values *Centella asiatica* for the preservation of memory and cognitive functions, since it is able to prevent neuronal degeneration, especially beta-amyloid. [14] In addition, *Centella asiatica* appears to have a neuroprotective effect on stroke-induced cognitive impairment and in Parkinson's disease. [15-17] Diabetic neuropathy, a widespread complication of diabetes mellitus, is currently treated with symptomatic therapies. *Centella asiatica*, which had already shown favourable neurotrophic effects in preclinical studies, [18] is now a potential candidate for the treatment of the reduction of neurological damage induced by diabetic hyperglycemia.

Other new insights that emerge from the review concern potentialities in the treatment of *Helicobacter pylori* infection [19] and induction of apoptosis on various types of tumour cells. [20-23]

*Centella asiatica* is also effective on the genesis of some inflammatory diseases such as psoriasis; [24] dermatologists use it for many skin conditions since it can inhibit the inflammatory pathways that contribute, at least in part, to the autoimmune degeneration of the skin.

The pre-clinical and clinical studies available (whether pivotal or randomized, double-blind and placebo-controlled), while confirming the already known properties of the plant, envisage new research scenarios and broader applications; these range from diabetic neuropathy to cardiovascular protection, from the treatment of burns to post-partum stretch marks. These areas could open new frontiers of research and development on a plant and its properties which have been known for some time but whose potential has been explored only in part.

A final but not inconsequential aspect is how the *Centella asiatica* supply chain is managed sustainably. Indena is sensitive to the importance of careful and accurate control of all supply chains and seeks ways of supporting the indigenous populations, for example by instigating social projects in one of the main harvesting areas of the plant, the Alaotra Mangoro region of Madagascar.

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# INDENA'S GLOBAL STRATEGY FOR BLUE LIGHT SKIN PROTECTION

Research has shown that blue light, similar to pollution, threatens our body every day and has a significant impact not only on eye health, as many people know, but also on the skin.

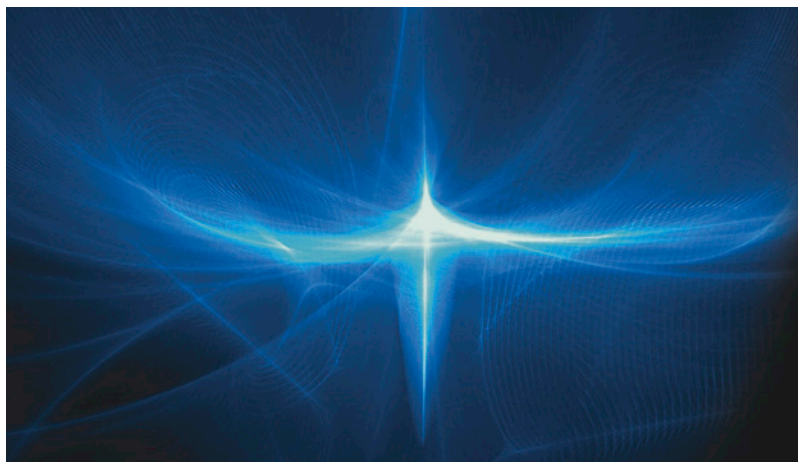
The main source of Blue Light of natural origin is the sun and exposure to sunlight, mainly due to its ultraviolet components, can lead to changes similar to the aging process. However, studies have shown that even the artificial blue light produced by LEDs, fluorescent light, TV screens, computers, tablets, smartphones etc. has a harmful impact on the skin. In particular, it has been observed that, similar to blue light occurring naturally, this artificial light produces oxidative stress and accelerates the aging process, mainly by inducing molecular damage to the proteins of the skin.

The habit of being always connected opens up new challenges for skin protection and Indena is ready to seize them through a global strategy of which Vitachelox™ is a fundamental pillar.

After demonstrating its effectiveness against the harmful effects of pollution, protecting the skin from pollutants and counteracting the formation of free radicals, the selection of optimized extracts has provided new evidence of its ability to significantly improve protein quality. In fact, a recent study of Vitachelox™ assessed its protective effect from damage produced by blue light on keratinocytes.

The validation method used provides evidence that blue light causes carbonylation of the proteins in keratinocytes, inducing functional damage at cellular level. The result of the study indicates the considerable protection activity of Vitachelox™ from the formation of carbonylated proteins - when used as an indicator of the damage produced by blue light - is significantly higher (results are included in a range between + 78% and + 82%) than the N-acetyl cysteine benchmark, in terms of effectiveness in protection against such light damage. These findings are very significant, especially considering the fundamental role of proteins on cellular mechanisms.

The safety and efficacy profile of Vitachelox™ is supported by numerous experimental tests; the synergical effectiveness of the extracts is patent protected. Professional competence and a rigorous innovatory approach to research have always been the hallmarks of Indena and have enabled the company to produce the highest quality botanical extracts of which Vitachelox™ is a notable example.





## News

# GROWING OLD HEALTHILY IN CHINA

Indena's Product Research Manager, Antonella Riva, spoke about healthy aging during the opening day of the 6th New Nutrition-Leading Summit, held in Beijing in June.

Aging was in fact the theme of the day, and Antonella focused on the crucial role in maintaining health of the non-essential secondary metabolites found in edible plants. It was an opportunity to showcase the quality of Indena and two of its products, Meriva® and Enovita®, outlining the scientific research that underpins them and the scientific rigour which is at the heart of the company's business.



Dr Riva was joined by her colleague Lisa Zhou of Indena's Chinese branch who acted as interpreter to translate her address into the language of the audience, made up of about 500 people coming from R&D and Marketing.

Participants were offered an opportunity to meet after the talk at a stand set up in collaboration with INFOARK. The presence of our researchers made a significant scientific contribution to this important international event as well as providing a further occasion for Indena to place a global spotlight on its company culture.



## CULTURE OF SAFETY PLAYS VITAL ROLE AT INDENA SITES

The OHSAS 18001 (Occupational Health and Safety Assessment Series) is one of the international certifications related to the management of health and safety at work.

It contributes to the implementation of a process of continuous performance improvement, based on the identification and classification of any dangers, together with a structured action plan aimed at eliminating, decreasing or preventing them. Both the Indena Tours site and, for the first time, the Bennett factory have passed the audit to obtain certification.

Bennett also obtained ISO 14001, having reached the world's most widespread environmental management systems standards. These also are based on a system which envisages planning, execution and control phases as well as putting improvements in place which seek to identify, document and monitor the environmental impact of an organization.

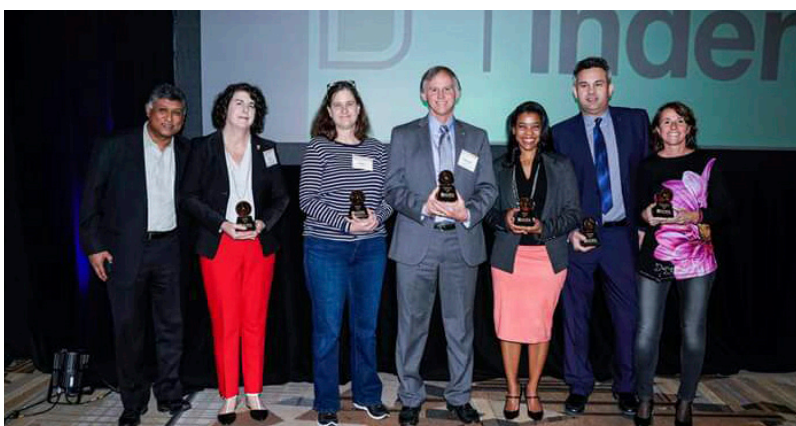
Due recognition goes to the commitment of Indena personnel in both plants for achieving this result. At all levels and in all areas of activity, this is an integral part of the culture of continuous improvement of health, safety and the environment.

## DOUBLE SUCCESS FOR INDENA IN THE AHPA AWARDS

The AHPA Herbal Industry Leader Award was presented to Indena at this year's Natural Products Expo West. Established in 2006 by the American Herbal Products Association, prizes are given annually to members of the association - individuals and organizations - who have contributed substantially and positively to the progress of the botanicals industry.

The Herbal Industry Leader Award category recognises companies which exemplify exceptional business practices. The association also conferred its Herbal Hero Award on the AHPA GACP-GMP Working Group, which includes two Indena experts, Alessandra Storzini and Paolo De Bellis. This award is given to people who have made an exceptional contribution to the AHPA committee or initiatives.

Throughout its history, Indena has always striven for excellence not only in research and production but also through collaboration with authoritative international experts. These two awards are a further recognition of that daily unceasing commitment.



## ORGANIC CHEMISTRY PRIZE ONCE AGAIN GOES TO INDENA

On behalf of Indena, R&D Director Pietro Allegrini received the prize for organic chemical research carried out in an industrial environment. The award, presented at the annual CDCO congress, is given each year by the organic chemistry division of the Italian Chemical Society, after a careful assessment by the divisional board of the candidatures put forward by the scientific community.

Pietro Allegrini was in fact awarded the Organic Chemistry Research Prize for the Development of Processes and Products in the Industry, for the results obtained from research aimed at clarifying the ambiguous dualism between Technique and Rite, the subject of his much-appreciated lecture.

Other Indena researchers have received this award in past years, demonstrating that research and development has always been a pillar for the company and will remain so in the future. The competence and professionalism of the people who work in this area has led to the achievement of excellent results, a judgement confirmed by the scientific community.



# UPCOMING TRADE SHOWS

## 2018/2019

### CPhI Worldwide

Madrid, Spain  
9-11 October 2018  
*Feria de Madrid*  
Stand 6B51

### SupplySide West

Las Vegas, U.S.A.  
6-10 November 2018  
*Mandalay Bay*  
Stand 5613

### Food Ingredients China

Shanghai, China  
18-20 March 2019  
*National Exhibition and Convention Center (NECCS)*  
Stand 61J62

### In-Cosmetics

Paris, France  
2-4 April 2019  
*Paris Expo Porte de Versailles*  
Stand C28

### Vitafoods

Geneva, Switzerland  
7-9 May 2019  
*Palexpo*  
Stand D14

### CPhI China

Shanghai, China  
18-20 June 2019  
*SNIEC Shanghai*  
Stand

### Vitafoods Asia

Singapore  
10-11 September 2019  
*Sands Expo & Convention Centre at Marina Bay Sands*  
Stand I36



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# INNOVATION SEMINAR

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## 2018

### Indena addresses new global health challenges

Cardiovascular health, gastrointestinal health and chronic silent inflammation: these are the most urgent public health issues, according to data to emerge from the most authoritative institutions in the world. And the focus was precisely on these very issues during a day of in-depth analysis promoted by Indena; the aim was to solicit an open and constructive discussion with some of the leading clinical experts, as part of a project which sees Indena at the forefront of creating company culture.

Constructive engagement with Academia and with clinical centres of excellence has proved to be a successful formula; effective in terms of bringing to the fore not only scientific research

but also the results that can be achieved by doing business in a concrete and innovative way, when the ultimate goal is quality. Quality is a very broad concept, but for Indena it has a precise meaning: quality is the commitment shown daily for almost a century to "design" and develop high-end botanical extracts, applying the same rigour required for work with pharmaceuticals to the production of extracts for nutrition and personal care. This means investment in research and development, highly qualified personnel, collaboration with scientists and professionals all over the world, if the company is to be always ahead of the game and second to none in innovation.

Among the main speakers at the Innovation Seminar held at Stresa in May were Attilio Giacosa, Scientific Coordinator at the Department of Gastroenterology at the

Policlinico di Monza, Andrea Poli, President of the Nutrition Foundation of Italy, and Francesco Visioli, Professor of Human Nutrition at the University of Padua. They presented their latest findings and discoveries regarding functional gastrointestinal disorders, cardiovascular health and silent inflammation, bringing new perspectives and solutions for their effective management, in particular through supplementation with botanical extracts. In response, Indena experts Pietro Allegrini R & D Director, Elisabetta Frattini R & D Researcher and Marketing Director Cosimo Palumbo brought to the table the direct experience of the company.

They highlighted the most recent scientific evidence to support the safety profile and effectiveness of some of Indena's botanical ingredients particularly rich in active principles and with excellent bioavailability, useful for cardiovascular health (Vazguard™, Bergamot Phytosome®), gastrointestinal health (artichoke leaves and ginger extracts Prodigest® and Casperome®, Boswellia Phytosome®), and the modulation of inflammation (Meriva®, Curcumin Phytosome®).

For years now, the demand for natural and botanical products has been relentless as

consumers seek products which help maintain a good general state of health and make prevention effective. There is a growing need for scientifically supported facts and figures, to enable an informed choice: younger consumers, in particular, are becoming more knowledgeable about "wellness" supplements. They expect products backed up by transparency, scientific evidence and validation profiles, obtained from production chains and processes carried out following best practices and intended for dietary use.

Nature is as ever an invaluable source of substances capable of giving new perspectives in maintaining a healthier and longer life and scientific literature confirms the potential role of well tolerated natural products in coping with many disorders. Quality remains the key point: only a rigorous scientific approach and serious commitment to quality in all areas, from plantation to extract, can guarantee the highest levels of authenticity of the integrators through checks and certification, areas in which Indena is preminent.

The following pages feature arguments which emerged during the Indena Innovation Seminar.





## New scenarios in the prevention of functional gastrointestinal disorders

**Abstract by Attilio Giacosa, Scientific Coordinator of the Department of Gastroenterology at the Policlinico di Monza, with comment by Elisabetta Frattini, Indena Researcher**

Functional Gastrointestinal disorders (FGID) refer to a group of conditions characterized by chronic abdominal discomfort with no apparent structural or biochemical cause to explain the symptoms. They are very common and affect about 60% of the world's population. The causes, pathophysiology and treatment of FGID are the focus of various lines of research, all of which take into account diet, genetics, neuromuscular function and immunological response. Aspects of mucosal inflammation, dysmotility and microbiome appear to be strongly involved in the pathogenesis of FGID. The most common gastrointestinal functional disorders are functional dyspepsia (FD) and irritable bowel syndrome (IBS).

Multiple mechanisms such as abnormal gastric emptying, bowel hypersensitivity, low gastric adaptation and the central nervous system are involved in FD. Symptoms include abdominal pain, swelling, bloating, early satiety, belching and nausea.

The signs and symptoms of IBS include spasms, abdominal pain, swelling, flatulence, diarrhoea or constipation or both. The pathophysiology of IBS includes the deterioration of gastrointestinal motility, intestinal hypersensitivity, poor communication between the intestinal and central nervous systems, persistent inflammation following acute infection of the intestine.

Pharmacological therapies available for FD and IBS are still as yet limited. Due to the influence of inflammation and dysmotility in the pathophysiological development of FGID, there is increasing interest in the potential

therapeutic role of artichoke leaf extract and ginger extract in the treatment of FD and turmeric and *Boswellia serrata* extracts in the treatment of IBS. Colonic diverticulosis affects about 70% of people in their eighties in the Western world. Although it is not a functional gastrointestinal disorder, recent data have shown micro-inflammatory changes in the diverticular mucosa, which means the two extracts may be considered as an alternative to mesalazine in future therapeutic treatments.

There has been recent research interest in Small Intestinal Bacterial Overgrowth, (SIBO), a clinical condition strongly linked to a number of gastrointestinal symptoms such as flatulence, bloating, diarrhoea, abdominal pain or spasms and occasional constipation; symptoms which may be associated with various risk conditions such as structural and anatomical changes due to surgery, motility disorders, irritable bowel syndrome, metabolic alterations (diabetes), organ dysfunction in the elderly (celiac disease, Crohn's disease), pharmacological therapies (recurrent use of antibiotics or gastric suppressors). Antibiotics are the first-line drugs to combat SIBO, but the high recurrence rate of these disorders suggests the potential role of well-tolerated natural products such as turmeric and *Boswellia* extracts, due to their beneficial effects associated with probiotics. Various studies have shown these probiotics to have a beneficial effect on health, probably due to the positive effects on microbiota, metabolism and immunomodulatory functions. The possibility of a positive influence on the microbiome is a crucial factor for health, since the microbiome seems to have effects on aging, digestion, the immune system, mood changes, as well as on cognitive functions.

*Meriva®*, *Casperome®* and *Prodigest®* are Indena's answer to gastrointestinal disorders; they confirm the hypothesis that some botanical extracts may be a useful supplement in improving these conditions. *Prodigest®* is a patented combination of standardized artichoke leaves and ginger extracts, which has given interesting results in this connection, due to the synergistic action of its components for healthy digestion. It is an excellent example of how

*an innovative approach supported by a solid scientific background can lead to a pioneering solution, a natural prokinetic. (1) Taken before meals, it relieves symptoms over a period of 14 days and this benefit lasts up to 28 days, as shown by a recent study in which 86% of the subjects enlisted reported an improvement in symptoms, 63% of them markedly so. (2) The discovery of the potential of Casperome® in gastrointestinal health is more recent. Its activity in the relief of numerous conditions related to inflammatory states such as neuropathic pain and the reduction of pain and edema associated with intense sporting activity had already been explored and consolidated. Recently, the Indena phytosome of *Boswellia serrata* has revealed enormous potential also in gastrointestinal health, as it can relieve the symptoms of IBS, and reduce discomfort in patients with ulcerative colitis in remission. (3,4) Early studies on the possible synergy between Casperome® and probiotics have yielded positive results. Also Meriva®, Indena's turmeric phytosome, which is able to alleviate inflammatory conditions, has given very positive results in clinical studies aimed at investigating the efficacy profile in gastrointestinal disorders. In particular, Meriva® has been found to be effective after 8 weeks of supplementation in maintaining the integrity of the gastrointestinal barrier and in improving the state of the liver in patients with Non-Alcoholic Fatty Liver Disease (NAFLD). (5-7)*

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## Preventing dyslipidemia with bergamot polyphenols

**Abstract by Andrea Poli – President of Nutrition Foundation of Italy, with comments from Pietro Allegrini, R&D Director at Indena**

Blood fat control is one of the main goals of cardiovascular prevention and certain basic concepts in this regard have been established. First of these concepts is that LDL lipoproteins are causally involved in atherogenesis. The risk of coronary heart disease (CHD) is greater when LDL levels in the blood increase, and decreases with each reduction of these levels, regardless of how this reduction was achieved.

According to a recently published meta-analysis, attempts to lower cholesterol produce better results when LDL levels before treatment are high or very high; in any case, these attempts reduce the risk of CHD, albeit less effectively, when baseline levels are low.

The second concept is that the role of HDL lipoproteins has been reconsidered; many studies now suggest that these lipoproteins may simply be risk indicators without causal links to atherogenesis.

Mendelian randomized trials have shown that cardiovascular risk is not changed in the presence of genetic alterations that induce an isolated increase in HDL. As a consequence, the real significance of dietary or pharmacological interventions aimed at increasing HDL levels remains uncertain. Lastly, there is ongoing debate on the role of triglycerides and the lipoproteins (VLDL) that transport them in atherogenesis. The current prevailing opinion is that, if blood levels are high, cardiovascular risk can increase and keeping them under control can have a positive effect on that risk.

Contrary to popular belief, attempts to control cholesterol by dietary means have a limited impact on LDL, the key lipid that determines the risk of CHD.

Therefore, doctors should consider complementary treatments such as food supplements if it is deemed that a patient's LDL cholesterol and cardiovascular risk are high, irrespective of whether or not the patient has reached the cardiovascular risk threshold for pharmacological treatment. When implemented appropriately, such treatments can greatly reduce cardiovascular risk over time, affecting the so-called "area under the curve" of the relationship between LDL cholesterol and cardiovascular risk during a lifetime. However, it is crucial that any supplements be recommended by a doctor, on the one hand to subjects carefully identified as suitable for treatment and, secondly, to improve patient compliance with therapy over time, as well as to avoid any possible drug interactions and side effects.

*An edible plant that has an excellent potential for use in the prevention of cardiovascular disease is bergamot, in particular the Citrus bergamia Risso et Poiteau, a plant endemic to Calabria. Its juice has a high percentage of flavonoids and above all a polyphenol pattern almost unique in nature. The composition of Bergamot extract is exceptional, and has shown antioxidant properties, hypoglycemic and hypolipidemic activity, effective in the modulation of the metabolic syndrome and in the prevention of cardiovascular disorders.*

*Indena has committed R&D resources to developing VAZGUARD™ which has been created with the application of the food grade delivery system Phytosome® to a highly standardized extract of the polyphenolic fraction of bergamot. VAZGUARD™ is standardized to contain 11-19% of bergamot flavonones (HPLC method) and its formulation optimizes the bioabsorption of polyphenols usually characterized by low solubility in water and in organic solvents. It is effective in reducing cardiovascular risk through modulation of total cholesterol, LDLs, triglycerides and blood glucose.*

*These findings have emerged in a recent double-blind, placebo-controlled randomized study, in which individuals with hyperglycaemia associated with hyperlipidemia took 1000mg of the extract for 30 days. (1)*

*Indena has succeeded in meeting the need for an extract with excellent bioavailability, exceeding the limits that nature sometimes imposes, so that it can be used safely and continuously in the prevention of cardiovascular diseases.*

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## The role of curcumin in the daily management of silent inflammation Inflammaging: genesis and solutions

*Abstract by Francesco Visioli, Professor of  
Human Nutrition at the University of Padua*

Understanding and controlling inflammatory mechanisms has become a key objective for clinical research. After decades of study, debate and discussion, researchers now understand that inflammation is closely linked to certain habits of Western societies and, above all, that it is statistically related to certain metabolic and chronic conditions linked to aging, such as cardiovascular diseases, diabetes and neurological disorders. Aging of the population is an unstoppable phenomenon that has now assumed global dimensions, with a massive socio-economic impact on National Health Services in countries throughout the world. It is characterized by an increase in the concentration of inflammatory markers in the blood, a phenomenon that has been called "*inflammaging*" and which is correlated to cognitive decline and mental health, alterations in the cellular composition of the body, loss of mobility, decline of the immune system with a consequent increase in susceptibility to infections, with insulin resistance and the development of type 2 diabetes, with atherosclerosis, vascular diseases and neoplastic generation. Acute inflammation is indeed a normal physiological response, essential to maintaining homeostatic control, but when it becomes chronic then it contributes to the physiopathology of numerous diseases.

Is it possible then, safely effectively and over time, to use nutrition to act on inflammation? Professor Visioli thinks so and has drawn on numerous studies to confirm it, in particular recent work on the use of turmeric extract. These studies provide the scientific rationale to support the use of the extract in the control

of inflammation and link it to improving health and well-being in many conditions.

Turmeric is already and will continue to be an outstanding example in the category of dietary supplements, not only because it has become popular among consumers, but also because of the potential of application that it continues to reveal in various fields, not least with cognitive disorders and gastrointestinal health. Being an extract that acts on chronic silent inflammation, it is envisaged for long-term intake. Producers therefore should show their commitment to testing the tolerability of their extracts over time. Indena has invested highly over the years in the research and development of a bioavailable form of turmeric extract with the result that today Meriva® Curcumin Phytosome® can be defined as a benchmark for the way it is able to manage inflammatory processes. Meriva® not only contains all three curcuminoids of turmeric, in the same proportions found in nature, but it is the completely food grade formulation that allows the highest plasma levels of DMC, the most powerful curcuminoid.

The dose of curcuminoids per 1g of Meriva® is 200mg, which perfectly corresponds to the average daily intake amongst the populations of India. This parameter is clinically validated by over 30 studies conducted in 10 different areas of well-being, which demonstrate not only the effectiveness of Meriva® but also the very high tolerability profile in the long run. The Curcumin Phytosome® formulation is 100% food grade, without any recourse to chemical additives. This is how Meriva® optimizes bioavailability and bioabsorption, respecting three fundamental criteria: effectiveness, long-term tolerability and safety.

The clinical and scientific evidence on humans confirms that it is an appropriate ingredient for a lasting health maintenance strategy, which is why Meriva® can be considered in every way The Life Guardian™.



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